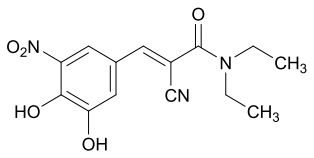
Entacapone

エンタカポン



$C_{14}H_{15}N_3O_5$: 305.29

(2*E*)-2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*,*N*-diethylprop-2-enamide

[*130929-57-6*]

Entacapone contains not less than 98.0% and not more than 102.0% of Entacapone ($C_{14}H_{15}N_3O_5$), calculated on the dried basis.

Description Entacapone occurs as a yellow to greenish yellow crystalline powder.

It is sparingly soluble in methanol, slightly soluble in ethanol (99.5), and practically insoluble in water.

It shows crystal polymorphism.

Identification **(1)** Dissolve 35 mg of Entacapone in 200 mL of methanol. To 7 mL of this solution add 0.1 mol/L hydrochloric acid TS to make 100 mL. Determine the absorption spectrum of this solution as directed under Ultraviolet-visible Spectrophotometry *<2.24>*, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Entacapone RS prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared absorption spectrum of Entacapone as directed in the potassium bromide disk method under Infrared Spectrophotometry *<2.25>*, and compare the spectrum with the Reference Spectrum or the spectrum of Entacapone RS: both spectra exhibit similar intensities of absorption at the same wave numbers.

Purity **(1)** Heavy metals－Dissolve 1.0 g of Entacapone in 20 mL of a mixture of methanol and *N*,*N*-dimethylformamide (3:1), and use this solution as the sample solution. Separately, weigh exactly 0.400 g of lead (II) nitrate, dissolve in water to make exactly 250 mL. Before use, dilute this solution with water to make 10 times the initial volume, then dilute this solution with water to make 10 times the initial volume. To 1.0 mL of this solution add a mixture of methanol and *N*,*N*-dimethylformamide (3:1) to make 20 mL, and use this solution as the standard solution. To the sample solution and standard solution add 2 mL each of acetate buffer solution (pH 3.5), mix, add 1.2 mL each of thioacetamide TS, and mix immediately. Allow them to stand for 2 minutes, filter through a membrane filter with a pore size of 0.45 μm, wash with methanol, and compare the colors on the membrane filters: the color obtained from the sample solution is not darker than that obtained from the standard solution (not more than 10 ppm).

(2) Halides－Being specified separately when the drug is granted approval based on the Law.

(3) Related substances－Dissolve 50 mg of Entacapone in 50 mL of a mixture of methanol and tetrahydrofuran (7:3), and use this solution as the sample solution. Pipet 5 mL of the sample solution, and add a mixture of methanol and tetrahydrofuran (7:3) to make exactly 50 mL. Pipet 5 mL of this solution, and add a mixture of methanol and tetrahydrofuran (7:3) to make exactly 50 mL. Pipet 1 mL of this solution, add a mixture of methanol and tetrahydrofuran (7:3) to make exactly 10 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the following conditions, and determine each peak area by the automatic integration method: the peak area of the related substance A, having the relative retention time of about 0.8 to entacapone, from the sample solution is not larger than 1.5 times the peak area of entacapone from the standard solution, the area of the peak other than entacapone and the peak mentioned above from the sample solution is not larger than the peak area of entacapone from the standard solution, and the total area of the peaks other than entacapone and the related substance A from the sample solution is not larger than 2 times the peak area of entacapone from the standard solution.

Operating conditions－

Detector, column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay.

Time span of measurement: About 2.5 times as long as the retention time of entacapone, beginning after the solvent peak.

System suitability－

System performance: Proceed as directed in the system suitability in the Assay.

Test for required detectability: Pipet 5 mL of the standard solution, add a mixture of methanol and tetrahydrofuran (7:3) to make exactly 10 mL. Confirm that the peak area of entacapone obtained with 10 μL of this solution is equivalent to 35 to 65% of that obtained with 10 μL of the standard solution.

System repeatability: When the test is repeated 5 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of entacapone is not more than 5%.

Loss on drying *<2.41>* Not more than 0.5% (1 g, in vaccum, 60℃, 3 hours).

Residue on ignition *<2.44>* Not more than 0.1% (1 g).

Assay Weigh accurately about 50 mg each of Entacapone and Entacapone RS (separately determine the loss on drying *<2.41>* under the same conditions as Entacapone), dissolve each in a mixture of methanol and tetrahydrofuran (7:3) to make exactly 50 mL. Pipet 5 mL each of these solutions, add a mixture of methanol and tetrahydrofuran (7:3) to make exactly 50 mL, and use these solutions as the sample solution and the standard solution. Perform the

test with 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and determine the peak areas, A_T and A_S of entacapone in each solution.

$$\text{Amount (mg) of entacapone } (C_{14}H_{15}N_3O_5) = M_S \times A_T / A_S$$

M_S: Amount (mg) of Entacapone RS taken, calculated on the dried basis

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 300 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with phenylated silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25°C.

Mobile phase: Dissolve 2.34 g of sodium dihydrogenphosphate dihydrate in water to make 1000 mL, and adjust to pH 2.1 with phosphoric acid. To 540 mL of this solution add 440 mL of methanol and 20 mL of tetrahydrofuran.

Flow rate: 1 mL per minute.

System suitability—

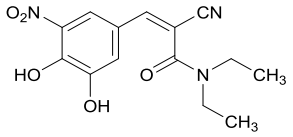
System performance: Dissolve 5 mg of Entacapone Related Substance A RS for System Suitability in a mixture of methanol and tetrahydrofuran (7:3) to make 25 mL. To 1 mL of this solution add a mixture of methanol and tetrahydrofuran (7:3) to make 20 mL, and use this solution as the solution for system suitability test. To 5 mL of the standard solution add a mixture of methanol and tetrahydrofuran (7:3) to make 50 mL. To 1mL of this solution and 1 mL of the solution for system suitability test add a mixture of methanol and tetrahydrofuran (7:3) to make 10 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, the related substance A and entacapone are eluted in this order with the resolution between these peaks being not less than 3.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of entacapone is not more than 1.0%.

Containers and storage Containers—Well-closed containers.

Others

Related substance A: (2*Z*)-2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*,*N*-diethylprop-2-enamide



Add the following to 9.01 Reference Standards (1):

Entacapone RS

Entacapone Related Substance A RS for System Suitability